



Fever and Systemic Inflammatory Response Syndrome Seen After Percutaneous Nephrolithotomy: Review of 1290 Adult Patients

Perkütan Nefrolitotomi Sonrasında Görülen Ateş ve Sistemik İnflamatuvar Yanıt Sendromu: 1290 Yetişkin Hastanın Gözden Geçirilmesi

PCNL, Ateş ve SIRS / PCNL, Fever and SIRS

Tulga Eğilmez, Mehmet Reşit Gören
Başkent Üniversitesi, Adana Uygulama ve Araştırma Hastanesi, Adana, Türkiye

Özet

Amaç: Minimal invazif olarak kabul edilmesine rağmen perkütan nefrolitotomi (PCNL) halen belirgin komplikasyon riski taşımaktadır. Yeni çalışmalar, sepsis insidansının daha önce bildirilenlerden fazla olabileceğini ileri sürmektedirler. Sistemik inflamatuvar yanıt sendromu (SIRS), hayatı tehdit eden bir komplikasyondur ve hastaların bir kısmında bakteriyemili veya bakteriyemisiz görülebilmektedir, SIRS gelişme riski ile postoperatif ateş epizodu arasındaki ilişkinin aydınlatılması bu çalışmanın amacıdır. **Gereç ve Yöntem:** PCNL ameliyatı uygulanan 1646 yetişkin hastanın medikal kayıtları gözden geçirilmiştir. Gerekli kriterleri taşıyan 1290 hasta çalışmaya alınmıştır. İstatistiksel analiz için gerekli çalışma değişkenleri tıbbi kayıtlardan elde edilmiştir. **Bulgular:** Taş yükü ile SIRS arasında anlamlı korelasyon bulunmaktadır ($p<0,05$) fakat ateş ile bulunmamaktadır. Hastaların komorbiditeleri tek başına ateş veya SIRS ilişkili değildir. Fakat ASA skoru 3 ve 4 ile SIRS istatistiksel korelasyon göstermektedir ($p<0,05$). Karşılaşılan 288 komplikasyonun büyük çoğunluğu Clavian 2. derece idi ve derecesi ≥ 2 komplikasyonlar hastahospitalizasyon süresini artırmaktadır ($p<0,05$). Ameliyat süresi >120 dk., ateş ve SIRS ile korele olan tek operasyon değişkenidir. Kan kaybı >2 gr/dL (Δ hemoglobin-Hb) ve Clavian 5 komplikasyonlar ateş ile istatistiksel anlamlı olarak koreledir. ASA skoru ≥ 3 , ameliyat süresi >120 dk., Δ Hb >2 gr/dL, taş boyutu ve Clavian 5 komplikasyonlar ile SIRS gelişimi arasında istatistiksel anlamlı korelasyon bulunmaktadır. 181 (%14) hastada görülen, ateş epizodunun ölüme götüren SIRS'a ilerleme insidansı %1,6 olarak tespit edilmiştir. **Tartışma:** Postoperatif ateşin hayatı tehdit eden bir duruma ilerleme riski düşüktür. Fakat kan kaybı 2 gr/dL'den fazla ve/veya ameliyat süresi 120 dakikadan fazla olması gibi diğer SIRS kriterlerine sahip hastalara özel önem verilmelidir. Çok az hastada görülmesine rağmen çoklu organ yetmezliği ile ölüme neden olabilmektedir.

Anahtar Kelimeler

Perkütan Nefrolitotomi; Sistemik Yangısal Yanıt Sendromu; Ateş

Abstract

Aim: Although accepted as minimally invasive, percutaneous nephrolithotomy (PCNL) still poses a significant risk of complications. Recent studies suggest that the incidence of sepsis may be higher than previously reported. The systemic inflammatory response syndrome (SIRS) seen in the subset of patients with or without bacteremia, is a life threatening complication and the purpose of this study is to give an insight to the relation between a post-operative fever episode and the risk of developing SIRS. **Material and Method:** Medical files of 1646 adult patients to whom a PCNL operation was performed were reviewed. A total of 1290 patients fulfilled the needed criteria and were included in the study. Study variables were recorded from the medical files for statistical analysis. **Results:** Stone burden had a statistically significant correlation with SIRS ($p<0.05$) but not with fever. Comorbidities of the patients alone did not have a correlation with fever or SIRS. But ASA score 3 and 4 showed statistically significant correlations with SIRS ($p<0.05$). Majority of the 288 complications encountered were Clavian grade 2 and grade ≥ 2 complications were seen to increase the hospitalization period ($p<0.05$). Operation time >120 min. was the only operative variable that had correlation with both fever and SIRS ($p<0.05$). Blood loss >2 g/dl (Δ haemoglobin-Hb) and Clavian 5 complications had statistically significant correlations with fever. ASA score ≥ 3 , operation time >120 min., Δ Hb >2 gr/dl, stone size and Clavian 5 complications had statistically significant correlations with the development of SIRS. The incidence of a fever episode, which was seen in 181 patients (14%), to progress to SIRS, which led to death, was found to be 1.6%. **Discussion:** Postoperative fever has a low risk of progressing to a life threatening condition. But special attention should be given to patients that also have the other SIRS criteria; blood loss more than 2 g/dl and/or operation time more than 120 minutes. Although only encountered in a small subset of patients, multiple organ dysfunctions can develop leading to death.

Keywords

Percutaneous Nephrolithotomy; Systemic Inflammatory Response Syndrome; Fever

DOI: 10.4328/JCAM.1949

Received: 25.06.2013 Accepted: 26.07.2013 Printed: 01.03.2015

J Clin Anal Med 2015;6(2): 196-201

Corresponding Author: Tulga Eğilmez, Dadaloğlu Mh. Serinevler 2591 Sk No:4/A, 01250 Yüreğir, Adana, Türkiye.

T.: +90 3223272727 F.: +90 3223271274 E-Mail: tulgaegilmez@yahoo.com

Introduction

The routine management of renal stones has been changed over the past decades and open surgery is now rarely necessary with the successful use of percutaneous nephrolithotomy (PCNL) for the treatment. Meanwhile, morbidity and mortality of renal stone disease and also of the treatment itself, has been dramatically reduced as the practice of PCNL has been perfected. Today, PCNL plays an integral role in managing renal stone disease. On the other hand, although accepted as minimally invasive, it is an operation which still poses a significant risk of complications. Clavien system has been modified to grade these complications [1, 2].

Among the complications, febrile and infectious complications are commonly seen but sepsis has been reported to be rare. In the literature, sepsis rates of PCNL have been reported to be between 0.25 to 1.5% [3]. But more recent studies suggest that the incidence may be higher than previously reported [4, 5]. Kadlec et al. [4] have reported 49 complications in their total cohort of 125 patients and 18 (14.4%) of these were febrile and infectious complications. Sepsis developed in four (3.2%) of these patients. Wang et al. [5] have reported a septic shock incidence of 2.4% among 420 patients who underwent a PCNL procedure.

The systemic inflammatory response syndrome (SIRS) seen in the subset of patients with (sepsis) or without bacteriemia is a life threatening complication. SIRS and sepsis are considered to be present in patients, who have two or more of the following criteria,

- 1- Body temperature lower than 36°C or higher than 38°C.
- 2- Heart rate greater than 90 beats/min.
- 3- Respiratory rate greater than 20 breaths/min or PaCO₂ less than 32 mmHg.
- 4- White blood cell count (WBC) greater than 12x10⁹/L or less than 4x10⁹/L, or >10% immature (band) forms.

These physiologic changes should represent an acute alteration from baseline in the absence of other known cause for such abnormalities [6].

Because the manifestations of sepsis are the same as those of SIRS, to diagnose the situation as sepsis, it should be determined whether or not the symptoms are a part of the direct systemic response to the presence of an infectious process. The mechanism of SIRS is not completely understood but can cause organ dysfunction and death even after control of the infection [7]. The question 'should a post-operative febrile episode seen during the early postoperative period after PCNL be treated as a grade I complication and followed so or as a grade II complication and treated more aggressively keeping in mind that it might be a component of SIRS and may progress to grade IV or V?' is still not answered. This single institution retrospective chart review aims to provide an insight to this question.

Material and Method

Medical files of 1646 adult patients to whom a PCNL operation was performed between 8/2002 and 5/2012 were reviewed. Patients with confounding factors that would have predisposed to urinary tract infection (UTI) or urosepsis were excluded from the study. Exclusion criteria included patients with a stent, nephrostomy tube or indwelling catheter, fever before surgery, patients

with active UTI, internal problems that would affect SIRS criteria, contralateral renal or ureteric stone disease, second look PCNL and same session bilateral PCNL operations.

Data recorded from the medical files included: age, gender, stone size, stone location, presence of hydronephrosis, other concomitant disease, previous shock wave lithotripsy or renal surgery history, American Society of Anesthesiologists (ASA) score, subcostal or intercostal entry, number of access tracts made during the operation, dilatation type (Amplatz dilators/balloon dilatation), operation time, blood transfusion, complications, hospitalization time, residual stone status, pre-operative haemoglobin (Hb) and WBC, post-operative Hb and WBC, post-operative maximum and minimum body temperatures, post-operative maximum heart and respiratory rates, post-operative renal and blood culture results.

The kidney stones were diagnosed by intravenous pyelography and/or computerized tomography (CT). Stone size was measured as the surface area calculated according to the EUA guidelines using the two greatest vertical and horizontal dimensional measures seen on a plain x-ray of the kidney-ureter-bladder (KUB) [8]. Stones filling the renal pelvis and all of the calyces were defined as staghorn calculi and the area of each stone part located in the calyces and the pelvis was calculated separately and then added. The size of radiolucent stones were calculated by the same way but by the dimensions obtained from non-contrast computed tomography images.

Operation time was derived from the anesthesia chart and defined as the time elapsed in minutes from the induction of anesthesia until the insertion of nephrostomy catheter. The patients were grouped into 4 groups (30-60 min, 61-90 min, 91-120 min, and >120 min). The difference of haemoglobin (Δ Hb) was calculated by subtracting the hemoglobin value after surgery from the value obtained within a week before surgery. The patients were grouped into 5 groups (0-0.5, 0.6-1, 1.1-1.5, 1.6-2 and >2 gr/dl).

The patients were evaluated using a KUB performed on the morning after the procedure and a CT performed 1 month after the operation for the follow-up. Postoperative outcome was evaluated by post-operative CT and patients lacking it were also excluded from the study. The residual stone status was evaluated in three categories; stone free (SF), clinically insignificant residual fragments (CIRF, residual fragments smaller than 4 mm) and clinically significant residual fragments (CSRF, residual fragments larger than 4 mm). Success rate was defined as the sum of SF and CIRF.

The type of complication encountered was noted and then classified according to the modified Clavien System [1]. For any patient, only the complication of highest grade was analyzed. Hospitalization time was defined as the number of days the patient spent at the hospital starting from the day of surgery.

According to the elective endoscopic operation preparation protocol of our clinic, all patients included in the study had a pre-operative urine culture and were treated pre-operatively according to the antibiotic sensitivity tests. More than 105 organisms per milliliter detected on a urine culture were used to define an infection and the operations were performed only after achieving a negative urine culture. Again, according to the protocol, all patients received peri-operative prophylactic antibiotic treat-

ment before surgery on arrival at the operation theatre with an intravenous administration of 1 g Cephazolin, a first-generation cephalosporin antibiotic and the antibiotic treatment was continued post-operatively with intravenous Ciprofloxacin 200 mg, bid, during the first post-operative day (POD). If post-operative fever $>38^{\circ}\text{C}$ was encountered, urine cultures from the nephrostomy catheter and two blood cultures were obtained and the intravenous antibiotic treatment was continued. The treatment was later changed according to the antibiotic sensitivity of the cultures. Otherwise, in the case of an uneventful post-operative period, this treatment was continued with per os Ciprofloxacin twice a day for 5 days starting from the post-operative day 2. Patients with known drug allergies, patients under age 18 or with renal insufficiency are exceptions for the above-mentioned peri-operative and post-operative antibiotic treatments and for the standardization of the treatment, these patients were not included in the study.

Patients that did not have medical data of the above mentioned study variables were excluded from the study. A total of 1290 patients fulfilled the needed criteria and were included in the study.

Operations: All of the operations were performed in a single center under general anesthesia. After ureteral catheter insertion in the lithotomy position, the patients were tilted to prone position. The pyelocalyceal system was approached with the insertion of an 18-gauge Chiba needle under fluoroscopic guidance. Tract dilation was achieved either via Amplatz or a high pressure balloon dilator NephroMaxTM (Boston scientific) after placement of a safety guide-wire in place. At the end of the dilation, a 30F renal sheath (Microvasive, Natick, Massachusetts) was placed and rigid nephroscopy was performed. A pneumatic lithotripter was used for stone fragmentation. The stone fragments were mechanically extracted and a nephrostomy catheter (14-20F) was placed at the end of the operation. The nephrostomy catheter was withdrawn following an antegrade pyelography which was performed after the gross hematuria cleared. Abandoned procedures due to failure to obtain access or bleeding at the time of dilation were not included in the study.

Statistical analysis: Statistical analysis of data was performed with Statistical Package for Social Sciences (SPSS) 15.0 for Windows and in addition to descriptive statistical methods (mean, standard deviation), Chi-square and Mann-Whitney tests were used for qualitative and numerical data, as appropriate. P values <0.05 were considered to be statistically significant.

Results

Table 1 shows the demographic and clinical characteristics of the patients and stones. Patient age distribution was 48.1 ± 15.7 years (range 18-85 years). Stone burden had a statistically significant correlation with SIRS ($p<0.05$) but not with fever. Comorbidities of the patients alone did not have a significant correlation with fever or SIRS. But ASA score 3 and 4 showed significant correlations with SIRS ($p<0.05$).

Operation time >120 min. was the only operative variable that had correlation with both fever and SIRS (Table 2). The correlation was statistically significant for fever and also for SIRS ($p<0.05$).

Most of the fever episodes were seen during the first or second

Table 1. Pre-operative clinical data of the patients

Variable	Value	P value (fever)	P value (SIRS)
Gender (n/%)			
Male	737/57%	0.65	0.83
Female	553/43%	0.57	0.66
Patient age (years)			
Mean \pm SD	48.1 \pm 15.7	0.80	0.59
Range	18-85		
Main comorbidities (n/%)			
Diabetes Mellitus	218/17%	0.23	0.57
Cardiovascular disease	347/27%	0.29	0.83
Stone burden (mm ² /renal unit)			
Mean \pm SD	426.4 \pm 285.9	0.11	$P<0.05^*$
Hydronephrosis (n/%)			
Nil	127/10%	0.63	0.40
Mild	481/37%	0.46	0.67
Moderate-Severe	682/53%	0.48	0.44
Stone location			
Renal pelvis	426/33%	0.7	0.82
Lower pole calyceal	233/18%	0.17	0.38
Middle pole calyceal	39/3%	0.36	0.24
Upper pole calyceal	64/5%	0.62	0.12
Stones in multiple calyces	322/25%	0.23	0.32
Staghorn calculus	206/16%	0.14	0.28
ASA score (n/%)			
1	326/25%	0.34	0.65
2	802/62%	0.26	0.13
3	161/12%	0.78	$P<0.05^*$
4	1/ $<1\%$	0.46	$P<0.05^*$

Table 2. Operative data of the patients

Variable	Value	P value (fever)	P value (SIRS)
Operation time (min)			
Mean \pm SD	80,7 \pm 43,7		
Range	30-240		
30-60 min (n/%)	246/19%	0.36	0.33
60-90 min (n/%)	362/28%	0.18	0.14
90-120 min (n/%)	497/39%	0.17	0.11
>120 min (n/%)	185/14%	$P<0.05^*$	$P<0.05^*$
Number of percutaneous tracts (n/%)			
1			
2	947/73%	0.56	0.23
3	291/23%	0.33	0.39
	52/4%	0.12	0.25
Percutaneous access (n/%)			
Subcostal	1193/92%	0.87	0.74
Intercostal	97/8%	0.92	0.42
Dilation (n/%)			
Nephromax	1102/69%	0.13	0.30
Amplatz	488/31%	0.45	0.32
Intra-operative blood transfusion (n/%)	52 (4%)	0.11	0.20

POD and other than operation time, $\Delta\text{Hb} >2$ g/dl and Clavian 5 complications had statistically significant correlations with fever (Table 3). ASA score ≥ 3 , operation time >120 min., $\Delta\text{Hb} >2$ g/dl, stone size and Clavian 5 complications were the parameters which had statistically significant correlations with the development of SIRS.

A total of 288 complications (22.3%) were encountered and the majority was Clavian grade 2 (Table 3). Clavian grade ≥ 2 complications were seen to increase the hospitalization period ($p<0.05$). Bleeding, urine leakage, clot or small fragments causing obstruction, renal pelvic perforation, deranged renal function, fever, pulmonary edema, ileus, pneumothorax, hydrothorax, colon perforation, sepsis, perirenal abscess, arteriovenous fistula, pulmonary embolism and death were the complications encountered. Two of the pulmonary embolisms seen in the study

Table 3. Post-operative data of the patients

Variable	Value	P value (fever)	P value (SIRS)
Duration of nephrostomy catheter (days)			
Mean ± SD	2.4±1.06	0.75	0.49
Range	1-14		
ΔHb (g/dl)			
Mean ± SD	-2.5±1.02		
0-0.5 gr/dl (n/%)	90/7%	0.34	0.23
0.6-1 gr/dl (n/%)	460/36%	0.17	0.51
1.1-1.5 gr/dl (n/%)	165/13%	0.42	0.21
1.6-2 gr/dl (n/%)	262/20%	0.08	0.11
> 2 gr/dl (n/%)	313/24%	P<0.05*	P<0.05*
Post-operative WBC>12x10 ⁹ /L,<4x10 ⁹ , >10% immature forms (n/%)	645/50%	0.23	0.19
Post-operative respiratory rate >20/min, PaCO ₂ <32 mmHg (n/%)	606/47%	0.89	0.91
Post-operative heart rate >90 beats/min (n/%)	451/35%	0.73	0.22
Post-operative body temperature >38°C or <36°C (n/%)	181/14%	-	0.15
Patients fulfilling SIRS criteria (n/%)			
2 variable	181/14%	0.21	-
3 variable	129/10%	0.16	-
4 variable	64/5%	P<0.05*	-
Post-operative			
positive urine/blood culture (n/%)	61/5%	0.41	0.67
positive urine culture	48/4%	0.56	0.31
positive blood culture	36/3%	0.15	0.17
Post-operative positive urine/blood culture in the post-operative fever group	61/34%	0.12	0.26
Complication (n/%)			
Clavian 1	84/6.5 %	0.36	0.22
Clavian 2	145/11.2%	0.14	0.58
Clavian 3a	32/2.5%	0.53	0.15
Clavian 3b	21/1.6%	0.33	0.43
Clavian 4a	3/0.2%	0.13	0.21
Clavian 4b	-	-	-
Clavian 5	3/0.2%	P<0.05*	P<0.05*
Post-operative blood transfusion (n/%)	39 (3%)	0.11	0.08
Residual stone status (n/%)			
SF	931/72%	0.24	0.17
CIRF	149/12%	0.29	0.11
CSRF	210/16%	0.15	0.29
Success rate (SF+CIRF) (%)	84%	-	-

group were managed without the need of an intensive care unit (ICU) management and were classified as grade 2 complications. The remaining two were treated in the ICU and classified as Grade 4a. One of the three patients who died (0.2%, Clavian 5) had a staghorn stone disease and an ASA score 4 (renal failure, diabetes mellitus and hypertension). The operation time was 140 min. and was stone free at the end of the operation. The operation was uneventful and was performed through lower and middle calyx entries. But massive bleeding occurred after the renal sheath was removed and was treated with embolization of the bleeding lower pole accessory artery. The other two patients also had large stones, operation times > 120 min. and Hb loss more than 2 g/dl. But embolization was not performed and these patients were followed with blood transfusions. In all of the three patients, bleeding stopped but persistent fever was encountered in the post-operative period. They had all four of the SIRS criteria but the nephrostomy and blood cultures showed no microorganism growth. Their conditions deteriorated in spite of the administered broad spectrum antibiotics and medical treatment. Eventually multiple organ failure (MOF) developed leading to death.

Table 4. Post-operative data of the patients

Variable	Value	P value (fever)	P value (SIRS)
Duration of nephrostomy catheter (days)			
Mean ± SD	2.4±1.06	0.75	0.49
Range	1-14		
ΔHb (g/dl)			
Mean ± SD	-2.5±1.02		
0-0.5 gr/dl (n/%)	90/7%	0.34	0.23
0.6-1 gr/dl (n/%)	460/36%	0.17	0.51
1.1-1.5 gr/dl (n/%)	165/13%	0.42	0.21
1.6-2 gr/dl (n/%)	262/20%	0.08	0.11
> 2 gr/dl (n/%)	313/24%	P<0.05*	P<0.05*
Post-operative WBC>12x10 ⁹ /L,<4x10 ⁹ , >10% immature forms (n/%)	645/50%	0.23	0.19
Post-operative respiratory rate >20/min, PaCO ₂ <32 mmHg (n/%)	606/47%	0.89	0.91
Post-operative heart rate >90 beats/min (n/%)	451/35%	0.73	0.22
Post-operative body temperature >38°C or <36°C (n/%)	181/14%	-	0.15
Patients fulfilling SIRS criteria (n/%)			
2 variable	181/14%	0.21	-
3 variable	129/10%	0.16	-
4 variable	64/5%	P<0.05*	-
Post-operative			
positive urine/blood culture (n/%)	61/5%	0.41	0.67
positive urine culture	48/4%	0.56	0.31
positive blood culture	36/3%	0.15	0.17
Post-operative positive urine/blood culture in the post-operative fever group	61/34%	0.12	0.26
Complication (n/%)			
Clavian 1	84/6.5 %	0.36	0.22
Clavian 2	145/11.2%	0.14	0.58
Clavian 3a	32/2.5%	0.53	0.15
Clavian 3b	21/1.6%	0.33	0.43
Clavian 4a	3/0.2%	0.13	0.21
Clavian 4b	-	-	-
Clavian 5	3/0.2%	P<0.05*	P<0.05*
Post-operative blood transfusion (n/%)	39 (3%)	0.11	0.08
Residual stone status (n/%)			
SF	931/72%	0.24	0.17
CIRF	149/12%	0.29	0.11
CSRF	210/16%	0.15	0.29
Success rate (SF+CIRF) (%)	84%	-	-

The most common isolated microorganism from the renal pelvis cultures was Escherichia Coli (47%). Coagulase (-) staphylococcus (29%), Enterococcus (13%), Proteus (4%), Klebsiella (3%), Acinobacter (3%) and ≥2 microorganisms (1%) were the other microorganisms encountered. Blood cultures showed positivity in 48 patients and the isolated microorganisms were Escherichia Coli (44%), Enterococcus (29%) and Staphylococcus (27%). But neither the renal pelvis nor the blood cultures had significant correlations with fever (p=0.56 and p=0.15, respectively) or SIRS (p=0.31 and p=0.17, respectively). When investigated further, post-operative leukocytosis alone, did not predict a febrile episode or a positive culture (p= 0.23 and p= 0.28, respectively). The incidence of a fever episode, which was seen in 181 patients (14%), to progress to SIRS which led to death, was found to be 1.6%.

Discussion

The pathophysiology of SIRS and the events that lead to MOF are poorly understood. Studies have shown that the development of SIRS is associated with immunosuppression and a dysregulated inflammatory response in which an excessive generation of po-

tent proinflammatory cytokines and chemokines is present [9]. During sepsis, there is a shift in the redox (oxidation-reduction) balance toward the oxidant state. This seems to intensify the development of SIRS, MOF and septic shock suggesting that the regulation of inflammatory response is defective [10]. But many other factors have also been postulated to trigger SIRS, including products released from bacteria (lipoteichoic acid and bacterial lipopolysaccharide) as well as products from damaged cells released after ischemia-reperfusion or after blunt trauma, in which no infectious agent is involved [7]. The results of this study corroborate the hypothesis that probably a non-infectious mechanism is involved in the development of SIRS encountered after PCNL.

In a previously reported study by Chen et al. [11], the incidence of SIRS in 209 patients who underwent PCNL was reported as 23.4%. Number of tracts, blood transfusion, stone size and presence of pyelocaliectasis were identified as risk factors for the development of SIRS. Another study by Mariappan et al. investigated 52 patients with stones ≥ 2 cm and dilated pelvicalyceal systems to whom 1 week per os ciprofloxacin treatment was given as an extended antibiotic prophylaxis [12]. They found a 7% SIRS rate in these patients compared to 18% SIRS in the control group.

During PCNL, the decision to perform multiple tracts when needed, depends mostly on whether there is bleeding or not. The results of this study showed correlation of SIRS with neither the number of tracts nor blood transfusions. ASA score ≥ 3 , operation time >120 min, Δ Hb >2 g/dl, stone size and Clavian 5 complications were the parameters which had statistically significant correlation with SIRS. Operation time >120 min, Δ Hb >2 g/dl and Clavian 5 complications were the parameters which had statistically significant association with fever. Δ Hb more than 2 g/dl and an operation time more than 120 min. showed a statistical significant correlation both with fever and also with SIRS. Overt causes such as post-operative pain and blood transfusion can also cause some of the SIRS criteria such as tachycardia and fever and might have had an impact on the relatively high SIRS rate (29%) of this study. Due to the retrospective nature of the study, patients with tachycardia due to pain and patients with tachycardia as a component of SIRS could not be differentiated, but intra-operative and/or post-operative blood transfusion had no statistically significant correlation with fever and also none with SIRS. Post-operative leukocytosis alone did not predict a febrile episode or a positive culture.

Endoscopic instrumentation in the presence of stones can induce bacteremia and septic shock [5]. Previously, numerous studies have been made in hope to be able to predict sepsis with pre-operative bladder urine culture, renal pelvis urine or stone culture. The incidence of post-operative bacteriuria in patients undergoing PCNL without prophylactic antibiotics has been reported to be 20% and stone culture positivity as 35% [13]. Furthermore, in the same study, it has been shown that infection in the upper tracts (either renal pelvic urine or stones) has four times the risk of resulting in urosepsis after PCNL, especially with large stones (≥ 20 mm) or in dilated pelvicalyceal systems. Rao et al. [14] have reported a statistically significant association between pre-operative bacteriuria and the development of post-operative bacteremia. Their results showed bac-

teremia in 37% of patients with a positive pre-operative urine culture and 8% in those with a negative urine culture. But controversially, Fowler JE [15] has reported a 77.3% incidence rate of infected stone culture and found that only 12.5% of these patients have a positive urine culture obtained from the bladder. Other studies have also shown that pre-operative bladder urine is not a good predictor for post-operative bacteriuria or bacteremia and stone or renal pelvic urine cultures are better [13]. Fever incidence has been reported as 28.8% in a study in which the patients had negative urine cultures before the operation and who were treated with prophylactic antibiotics [16].

On the other hand, in this study group, when compared to these previous studies, although SIRS was encountered slightly more frequently, fever and positive cultures were seen less and positive cultures had no statistical significant correlation with SIRS. Patients fulfilling the SIRS criteria were 29% of the total 1290 patients. Fever was seen in 14% and positive urine and/or blood cultures were seen in only 5% (sepsis) of the patients. But it should be noted that post-operative cultures were only obtained from the patients who developed fever in the postoperative period. Positive cultures were seen in 34% of this patient group who had at least one post-operative fever episode. These results might be affected by the strict preparation protocol not allowing the operation to be performed until a negative urine culture is obtained, although it might be accepted as an over-treatment, the prolonged antibiotic use which was administered according to our protocol or by the culture results that might have been altered by the prophylactic antibiotics used.

Seitz et al. [17] have reported a 23.3% complication rate in their group of PCNL patients. When the literature is reviewed most of the complications encountered after a PCNL operation are low grade complications. Especially Clavian 1 and 2 complications have differences between institutions due to different antibiotic protocols. In an institution where antibiotics are administered post-operatively as a routine treatment are not accepted as a deviation from the normal pharmacological treatment. But in another institution where no post-operative antibiotics are routinely used, the same antibiotic treatment is graded as Clavian 1. Post-operative antibiotics were used routinely in this study group and Clavian 1 complications were encountered less than Clavian 2 complications (6.5% and 11.2%, respectively). The retrospective nature of the study may have limited the ability to capture some of the low grade complications. Again, in an institution where radiological interventions are regularly and successfully performed, a complication might be treated by interventional radiology and general anesthesia might not be needed (Clavian 3a). But in another institution, the same complication may have to be treated by surgery under general anesthesia (Clavian 3b). Under the shadow of these weak points of the Clavian system, complications were seen in 22.3% of the patients and most of them were low grade (smaller than Clavian 3a) and Clavian 3a and higher complications were seen in 4.5% of the patients.

All of the SIRS criteria including fever were present in all, but bacteriuria (renal pelvis) and/or bacteremia was seen in none of the 3 patients who died due to MOF suggesting that other mechanisms enrolled in SIRS play role in the process. Supporting this, Martin et al. [18] have reported bacteremia in only 50%

of their septic patient group. The results of this study suggest that a long traumatic operation for a large stone, causing a significant blood loss in a patient with co-morbidities that affect his/her life (ASA \geq 3) might trigger a non-bacterial mechanism of SIRS. The renal trauma caused by PCNL might be the reason of the excessive generation of pro-inflammatory cytokines and chemokines causing a dysregulated inflammatory response or a mechanism aggravated by a suppressed immune response might be involved [9, 10]. Further studies are needed to clarify the mechanism involved.

Conclusions

Fever which is mostly seen on the first or second post-operative days has a low risk of progressing to a life threatening condition. But special attention should be given to patients that also have all of the other SIRS criteria, big stone burden, blood loss more than 2 g/dl and/or an operation time more than 120 minutes. Although only encountered in a small subset of patients (1.6% of the fever group), even if the patient has a sterile pre-operative urine culture and is also under antibiotic treatment, multiple organ failure can develop leading to death.

Competing interests

The authors declare that they have no competing interests.

References

- de la Rosette JJ, Opondo D, Daels FP, Giusti G, Serrano A, Kandasami SV, et al. Categorisation of complications and validation of the Clavien score for percutaneous nephrolithotomy. *Eur Urol* 2012;62(2):246-55.
- Dindo D, Demartines N, and Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; 240(2):205-13.
- Menon M and Resnick MI. Urinary Lithiasis: Etiology, diagnosis and medical management. In: Walsh PC, editors. *Campbell's Urology*. Philadelphia: Elsevier Saunders; 2002.p.3229-30.
- Kadlec AO, Greco KA, Fridirici ZC, Hart ST, Vellos TG, and Turk TM. Comparison of complication rates for unilateral and bilateral percutaneous nephrolithotomy (PCNL) using a modified Clavien grading system. *BJU Int* 2013; 111(4 Pt B):E243-8.
- Wang Y, Jiang F, Wang Y, Hou Y, Zhang H, Chen Q, et al. Post-percutaneous nephrolithotomy septic shock and severe hemorrhage: a study of risk factors. *Urol Int* 2012;88(3):307-10.
- Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest* 1992;101(6):1644-55.
- Erridge C. Endogenous ligands of TLR2 and TLR4: agonists or assistants? *J Leukoc Biol* 2010;87(6):989-99.
- Turk C, Knoll T, Petrik A, Sarica K, Straub M, and Seitz C. *EAU Guidelines on Urolithiasis*. EUA, London; 2011.
- Ward PA. Immunosuppression in sepsis. *JAMA* 2011;306(23):2618-9.
- Bosmann M and Ward PA. The inflammatory response in sepsis. *Trends Immunol* 2013;34(3):129-36.
- Chen L, Xu QQ, Li JX, Xiong LL, Wang XF, and Huang XB. Systemic inflammatory response syndrome after percutaneous nephrolithotomy: an assessment of risk factors. *Int J Urol* 2008;15(12):1025-8.
- Mariappan P, Smith G, Moussa SA, and Tolley DA. One week of ciprofloxacin before percutaneous nephrolithotomy significantly reduces upper tract infection and urosepsis: a prospective controlled study. *BJU Int* 2006;98(5):1075-9.
- Mariappan P, Smith G, Bariol SV, Moussa SA, and Tolley DA. Stone and pelvic urine culture and sensitivity are better than bladder urine as predictors of urosepsis following percutaneous nephrolithotomy: a prospective clinical study. *J Urol* 2005;173(5):1610-4.
- Rao PN, Dube DA, Weightman NC, Oppenheim BA, and Morris J. Prediction of septicemia following endourological manipulation for stones in the upper urinary tract. *J Urol* 1991;146(4):955-60.
- Fowler JE, Jr. Bacteriology of branched renal calculi and accompanying urinary tract infection. *J Urol* 1984;131(2):213-5.
- Cadeddu JA, Chen R, Bishoff J, Micali S, Kumar A, Moore RG, et al. Clinical significance of fever after percutaneous nephrolithotomy. *Urology* 1998;52(1):48-50.
- Seitz C, Desai M, Hacker A, Hakenberg OW, Liatsikos E, Nagele U, et al. Incidence, prevention, and management of complications following percutaneous

nephrolitholapaxy. *Eur Urol* 2012;61(1):146-58.

18. Martin GS, Mannino DM, Eaton S, and Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med* 2003;348(16):1546-54.